Supplementary materials

Detailed Computational Methods

We examined correlations of outcome (survived/died) with all other available variables for all patients admitted to the ward, using the visualization tool *Mirador* (https://fathom.info/mirador/, Suppl. Figure 1) for exploratory analysis. We then conducted a univariate correlation analysis by calculating the P-value of the pairwise association between all demographic, clinical and laboratory variables available at presentation and outcome (survival or death), applying a χ^2 test with Yates correction for the binary variables, and point biserial correlation test for numerical.

With the purpose of model construction, we first set a limit on the number of predictors to avoid overfitting. Following a widely-accepted rule of thumb in multivariate regression modeling, this number should not exceed $M_{max}=N/10$,[1] where N is the minimum count over the two outcome categories (survived, died). In our data, N = 64, yielding $M_{max}\sim7$, which is much lower than the total number of variables in our dataset (47).

After removing variables with P-value of univariate association with outcome higher than 0.1, we still had a total of 22 potential predictor variables. To obtain a smaller saturated model, we applied the following data-reduction steps:

[1] Frank E. Harrell J. Regression Modeling Strategies: Springer; 2015.

1. Redundancy analysis with the function redun(), from the Hmisc package[2] in the R software, and hierarchical clustering of variables with the varclus() function, also provided by Hmisc. The function redun() determines what variables can be predicted from the remaining variables above a given R^2 cutoff using parametric additive models. We applied redun() with 0.3 as the R^2 cutoff, followed by varclus() with pairwise Hoeffding D statistic as similarity measure, on separate groupings of the original variables. The groups were: clinical signs/symptoms, demographics, vital signs, and laboratory variables. We then removed either redundant variables as determined by redun(), or variables that were part of a cluster with a Hoeffding distance greater than 0.3 in order to keep only one representative variable per cluster. We combined the remaining variables and applied an additional round of redun() followed by varclus() on all variables simultaneously to remove additional superfluous predictors.
2. Constructing a reduced saturated model using multiple imputation with aregImpute() from Hmisc and model fitting over imputed datasets with fit.mult.impute(), provided by the rms package.[3] The resulting model has 14 predictors, with a total log likelihood ratio (LR) χ^2 of 39.55. The estimated shrinkage of the model is S = (LR – p)/LR, with p being the number of parameters, so S = (39.55 – 14)/39.55 = 0.64. The recommended minimum shrinkage for a well calibrated model is above 0.8 or 0.9, so further reduction was needed.

[2] Harrel Miscellaneous package: https://cran.r-project.org/web/packages/Hmisc/index.html
[3] Regression Modeling Strategies: https://cran.r-project.org/web/packages/rms/index.html

3. Constructing a parsimonious model by selecting the "best" predictors in the reduced saturated model. We determined these predictors by ranking the variables by the P-value of their LR χ^2 in the saturated model, and choosing the top 7. These variables determined the predictors in the final parsimonious model.

We eventually constructed three regression models, the first incorporating age + clinical + laboratory variables (described in the main text), the second age + laboratory-only variables, and the third age + clinical-only variables. The same steps described above were applied to generate thee three models, however, the saturated model in each case was derived from the corresponding set of variables (clinical signs/symptoms, laboratory.) Predictor variables in the final parsimonious set could still be removed if the P-value of their LR χ^2 is higher than 0.1, so that the model could end up having fewer than 7 predictors, which was indeed the case in the age + laboratory and age + clinical models.

After defining the parsimonious models, we imputed missing values in the data using the MICE package for R, and also tested the validity of the Missing Completely At Random (MCAR) condition with the TestMCARNormality() function from R's MissMech package (Suppl. Figure 2). We generated 100 imputed datasets with MICE, and fitted each one separately using the glm() function in R. We finally combined the resulting 100 fitted models for each set of predictors into a single average model, equivalent to

averaging results from the individual models,[4] with the pool() function available in MICE. Outcome was missing for 7 patients that were discharged against medical advice so their outcome could not be determined. However, MICE can be applied to all variables, by indicating which one is the dependent and which ones the explanatory.[5]

We validated the models using bootstrap sampling. Each model was re-trained on 1,000 bootstrap replicates of each imputed dataset in order to obtain the optimism-corrected Area Under the Curve (AUC), Brier score, calibration error,[6] accuracy, and adjusted McFadden pseudo-R^2. We computed the optimism of each statistic by applying Efron's "0.632" method,[7,8] in which the model is refitted on each bootstrap sample, and applied to both the bootstrap training set and the left-out subjects (on average, each bootstrap sample contains 63.2% of the subjects, and hence the name of the method.) The difference between the two gives the optimism, which is then averaged over all the bootstrap iterations. We estimated the average and confidence intervals of the statistics over the multiple imputations with Fisher's transformation,[9] and generated the Receiver Operating Characteristic (ROC) and calibration curves and computed optimism-corrected Area Under the Curve (AUC), Brier score, calibration error, accuracy, and adjusted

[4] Miles A. Obtaining Predictions from Models Fit to Multiply Imputed Data. Sociological Methods & Research 2015.
[5] Azur MJ, Stuart EA, Frangakis C, Leaf P. Multiple Imputation by Chained Equations: What is it and how does it work? Int J Methods Psychiatr Res. 2011 Mar 1; 20(1): 40–49.
[6] Yaniv I, Yates JF, Smith JK. Measures of discrimination skill in probabilistic judgment. Psychological Bulletin 1991;110:611-7.
[7] Efron B. Estimating the Error Rate of a Prediction Rule: Improvement on Cross-Validation. Journal of the American Statistical Association 1983;78:316-31.
[8] Efron B, Tibshirani R. Improvements on Cross-Validation: The 632+ Bootstrap Method. Journal of the American Statistical Association 1997;92:548-60.

[9] Harel O. The estimation of R2 and adjusted R2 in incomplete data sets using multiple imputation. Journal of Applied Statistics 2009;36:1109-18.

McFadden pseudo-R^2 by performing "micro-averaging" (merging all the predictions from each bootstrap), and then "macro-averaging" over the 100 imputations. [10]

After the modeling stage, we investigated the clinical symptomatology of LF in more depth, guided by the parameters we observed in our regression models. Since we are particularly interested in kidney dysfunction and Acute Kidney Injury (AKI), we computed the Blood Urea Nitrogen to creatinine ratio (BUN:Cr) for all patients that developed AKI during treatment. This ratio can point to suspected causes for AKI:[11] a ratio greater than 20:1 is indicative of dehydration or hypoperfusion, while a ratio lower than 10:1 could indicate intrinsic renal damage. We estimated the BUN:Cr distributions for two groups of AKI patients: those with history of fluid loss (defined as presenting diarrhea, bleeding, or vomiting at admission) and those without (no signs of diarrhea, bleeding, and vomiting), by applying a Kernel Density Estimator (KDE) on each imputed dataset from a total of 100 multiple imputations generated with the MICE, using the default settings in the plot() function from the Pandas Python library. We also aggregated all imputations into a single dataset, which we used to generate two averaged distributions for AKI patients with and without history of fluid loss. We finally compared these distributions using the Kolmogorov-Smirnov (KS) test.[12]

Comparison with other regression models for LF

[10] Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the Performance of Prediction Models

[11] Hosten A. BUN and Creatinine. In: Walker HH, WD; Hurst JW, ed. Clinical Methods: The History, Physical, and Laboratory Examinations. 3 ed. Boston: Butterworths; 1990.

[12] Hollander M. Nonparametric statistical methods. 2nd ed. ed. New York: Wiley; 1999.

The only other logistic regression model for LF outcome was introduced by McCormick and colleagues in 1987.[13] They applied multivariate, stepwise logistic-regression to produce a model using temperature, vomiting, sore throat, and bleeding as predictors. When we trained a logistic-regression model on the ISTH data with these four predictors (Suppl. Table S2C), the model performed poorly (AUC = 0.55, R^2 = 0.07; Suppl. Table S3, Suppl. Figure S6), while McCormick reported >90% success rate in identifying fatal outcomes and good calibration with the observed rates (goodness-of-fit χ^2 = 90.1, P=0.001). This discrepancy highlights the difficulty in creating accurate models for the diverse LASV cases that can be generalized to different countries and sites. This difficulty is probably exacerbated here, as the cases reported by McCormick et al. were recorded 40 years ago, between 1977 and 1979, in two hospitals in Sierra Leone.

As we mentioned earlier, we also considered two alternative logistic regression models in our study, one including only laboratory biomarkers in addition to age, and the other only clinical features and age (Suppl. Tables S2A and S2B, Suppl. Figures S4 and S5); the latter model could be useful in settings with no access to laboratory data. They also perform well, with the age + laboratory-only model having an AUC of 0.85 and R^2 of 0.37, and the age + clinical-only model (Suppl. Table S3) having an AUC of 0.78, and an R^2 of 0.27.

Source code availability

[13] McCormick JB, King IJ, Webb PA, et al. A Case-Control Study of the Clinical Diagnosis and Course of Lassa Fever. *Journal of Infectious Diseases* 1987; 155(3): 445-55.

The R and Python scripts that implement the computational protocols of variable selection, model fitting and evaluation, as well as risk stratification, are available in the following GitHub repo, under an MIT license:

https://github.com/broadinstitute/lassa-isth-code

Supplementary Figures

Figure S1. *Mirador* tool for exploratory analysis. *Mirador* is a software tool to inspect correlations between any pair of variables in a dataset, using various visual representations (scatter plots, histograms, and eikosograms). It uses a Mutual Information-based test of statistical association to highlight those pairs that are significantly associated at a given P-value threshold. It is available for download free of charge at https://fathom.info/mirador/

Figure S2. Missing patterns in the data. The histogram on the left shows the fraction of missing values of each variable in the age + clinical + laboratory model, and the plot on the right the different missing patterns in the data. The Missing Completely At Random (MCAR) condition is not rejected at the 0.05 level, according to the

TestMCARNormality() function from R's MissMech package, which tests for equality of covariances between groups having identical missing data patterns.

Figure S3. Univariate analysis of signs/symptoms and laboratory variables. (A) box plots of laboratory biomarkers significantly associated with outcome ($P<0.05$), with the box representing the quartiles of the distributions of surviving and fatal cases, and the whiskers extending to the rest of the distributions with the exception of the outlier values. (B) signs and symptoms, ranked by decreasing incidence among fatal cases**.** (The characters on top of box plots in (A) and the bars in (B) indicate statistical significance according to the provided legends.

Figure S4. Performance plots for the clinical-only model. (A) ROC curve, (B) calibration curve, (C) sensitivity/specificity plot, and (D) risk groups.

Figure S5. Performance plots for the laboratory-only model. Same as in Figure S3.

Figure S6. Performance plots for the clinical-only model, with the variables used by McCormick. Same as in Figure S3.

Figure S7. Geographical distribution of the incidence of AKI. Population clusters were generated from the cases treated at ISTH between 2011 and 2015, and the area of the clusters made proportional to the number of cases in each one. The color gradient indicates the incidence of AKI in each cluster.

Figure S8: Plot of vitals during treatment for patients with and without AKI. Center dark line represents median value, shaded area extends between the 25 and 75% percentiles.

Figure S1

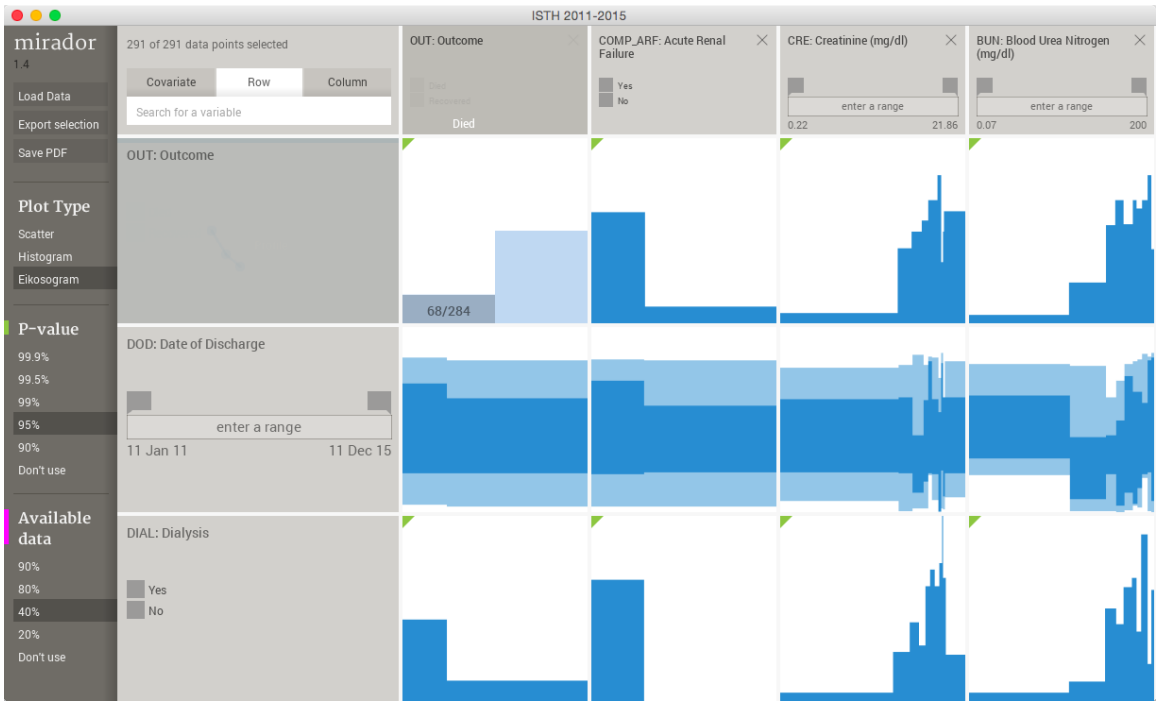

ISTH 2011-2015
mirador
1.4
Load Data
Export selection
Save PDF
Plot Type
Scatter
Histogram
Eikosogram
P-value
99.9%
99.5%
99%
95%
90%
Don't use
Available data
90%
80%
40%
20%
Don't use
291 of 291 data points selected
Covariate
Row
Column
Search for a variable
OUT: Outcome
DOD: Date of Discharge
enter a range
11 Jan 11
11 Dec 15
DIAL: Dialysis
Yes
No
OUT: Outcome
Died
COMP_ARF: Acute Renal Failure
Yes
No
CRE: Creatinine (mg/dl)
enter a range
0.22
21.86
BUN: Blood Urea Nitrogen (mg/dl)
enter a range
0.07
200
68/284

Figure S2

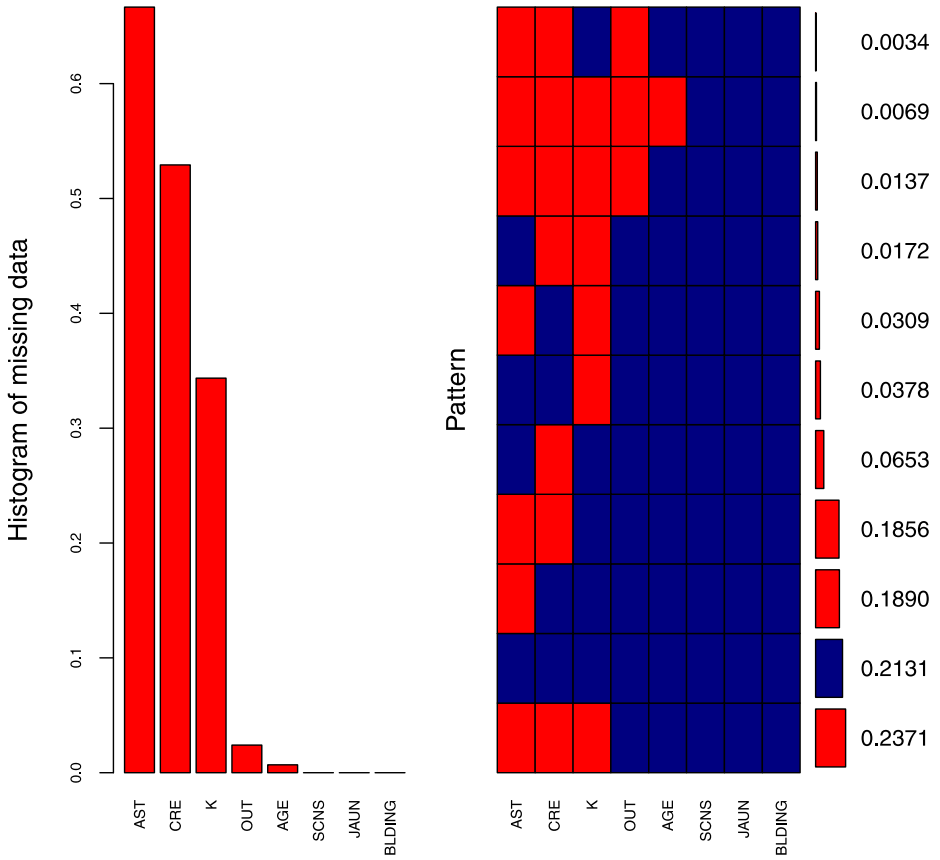

Histogram of missing data
0.0
0.1
0.2
0.3
0.4
0.5
0.6
AST
CRE
K
OUT
AGE
SCNS
JAUN
BLDING
Pattern
AST
CRE
K
OUT
AGE
SCNS
JAUN
BLDING
0.0034
0.0069
0.0137
0.0172
0.0309
0.0378
0.0653
0.1856
0.1890
0.2131
0.2371

Figure S3

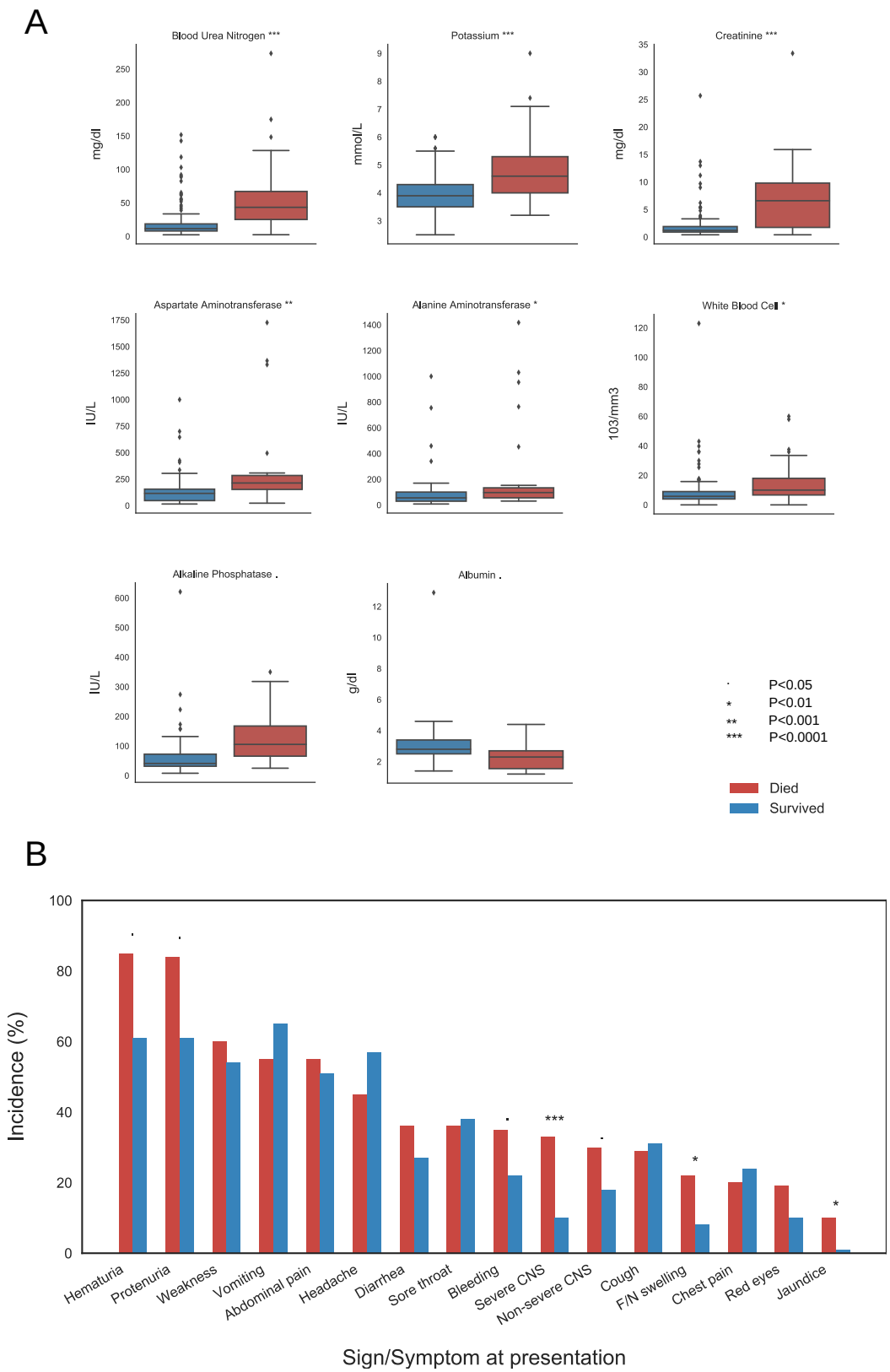

A
Blood Urea Nitrogen ***
mg/dl
Potassium ***
mmol/L
Creatinine ***
mg/dl
Aspartate Aminotransferase **
IU/L
Alanine Aminotransferase *
IU/L
White Blood Cell *
103/mm3
Alkaline Phosphatase .
IU/L
Albumin .
g/dl
. P<0.05
* P<0.01
** P<0.001
*** P<0.0001
Died
Survived
B
Incidence (%)
Hematuria
Proteinuria
Weakness
Vomiting
Abdominal pain
Headache
Diarrhea
Sore throat
Bleeding
Severe CNS
Non-severe CNS
Cough
F/N swelling
Chest pain
Red eyes
Jaundice
Sign/Symptom at presentation

Figure S4

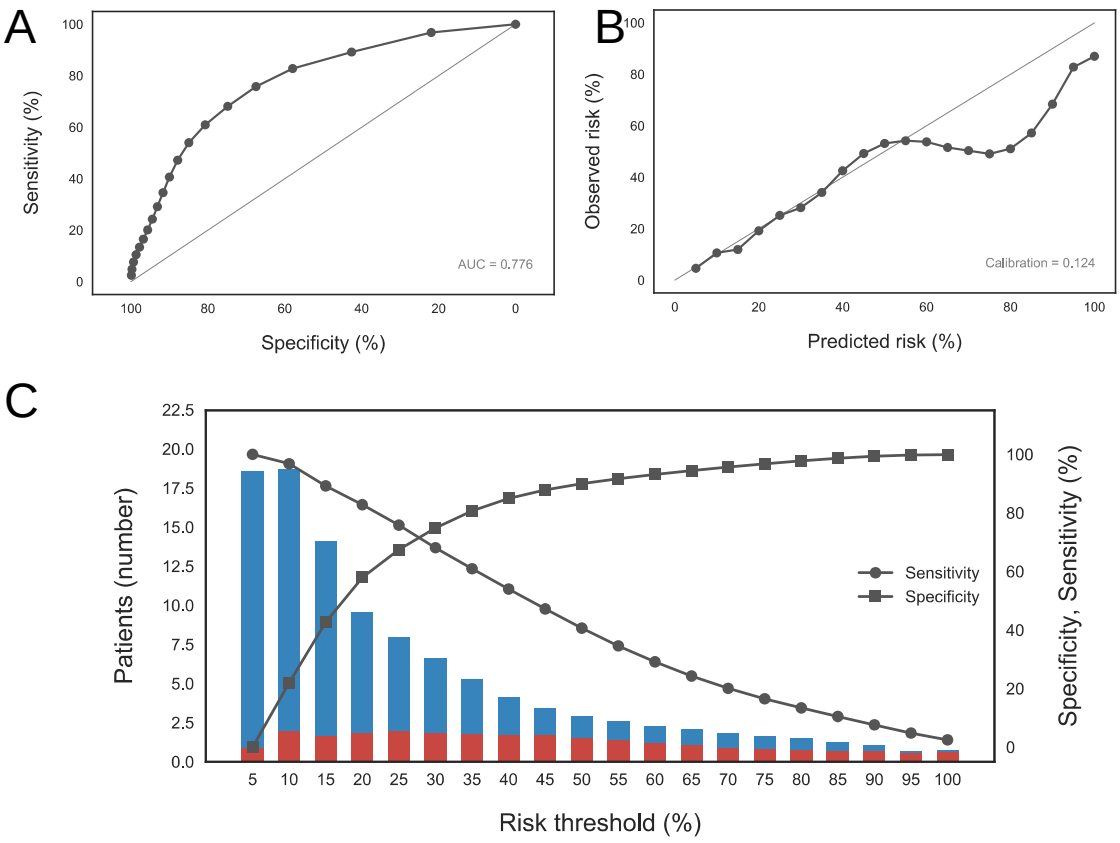

A
Sensitivity (%)
Specificity (%)
AUC = 0.776
B
Observed risk (%)
Predicted risk (%)
Calibration = 0.124
C
Patients (number)
Specificity, Sensitivity (%)
Risk threshold (%)
Sensitivity
Specificity

Figure S5

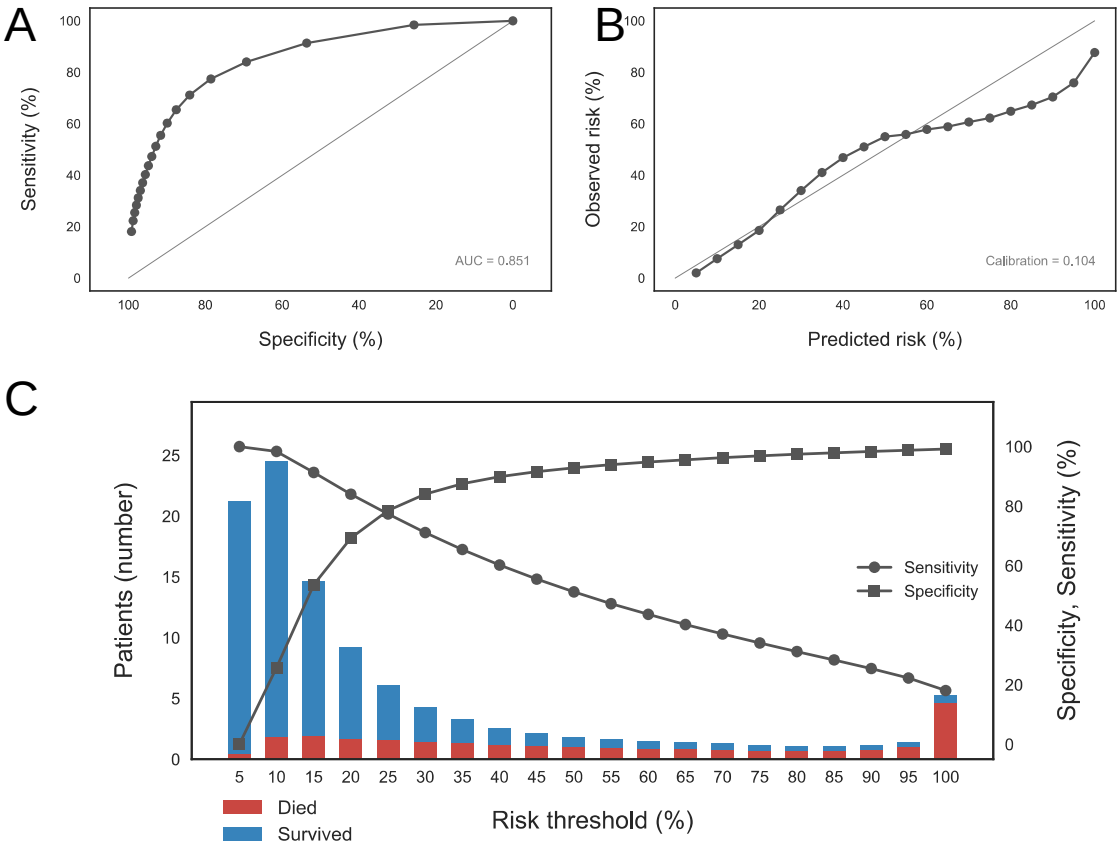

A
Sensitivity (%)
Specificity (%)
AUC = 0.851
B
Observed risk (%)
Predicted risk (%)
Calibration = 0.104
C
Patients (number)
Specificity, Sensitivity (%)
Risk threshold (%)
Sensitivity
Specificity
Died
Survived

Figure S6

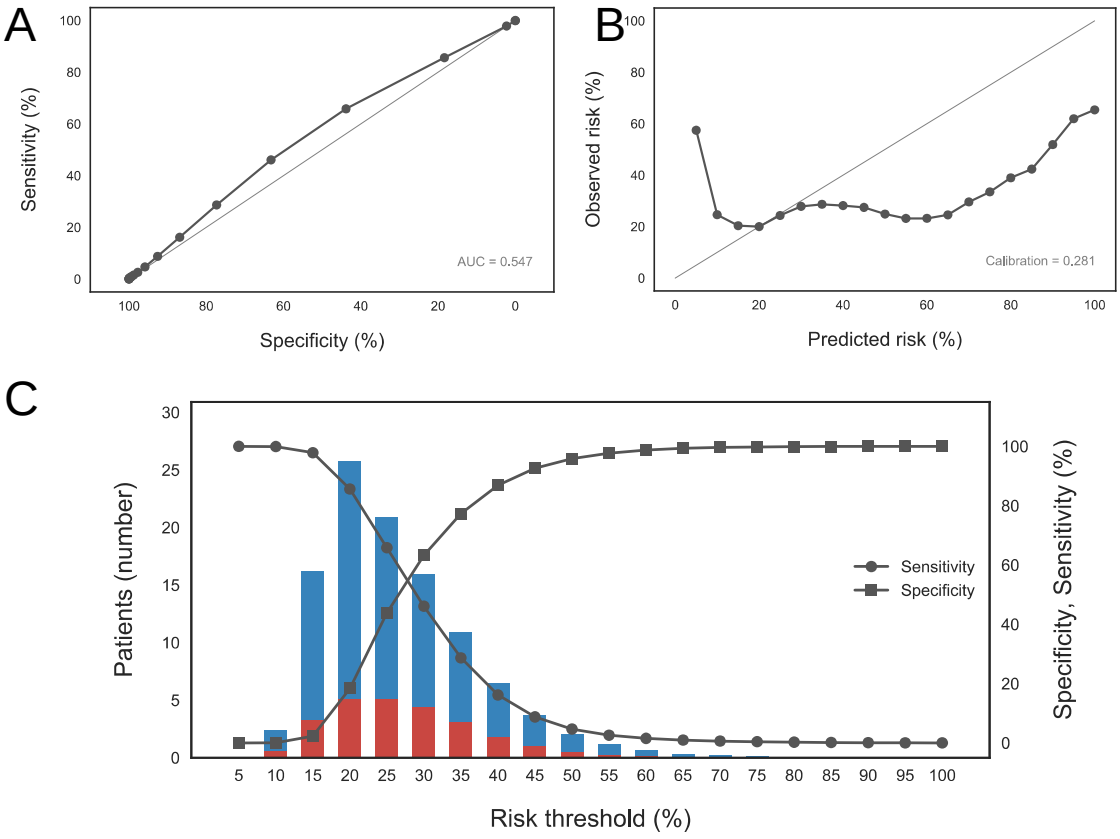

A
Sensitivity (%)
Specificity (%)
AUC = 0.547
B
Observed risk (%)
Predicted risk (%)
Calibration = 0.281
C
Patients (number)
Specificity, Sensitivity (%)
Risk threshold (%)
Sensitivity
Specificity

Figure S7

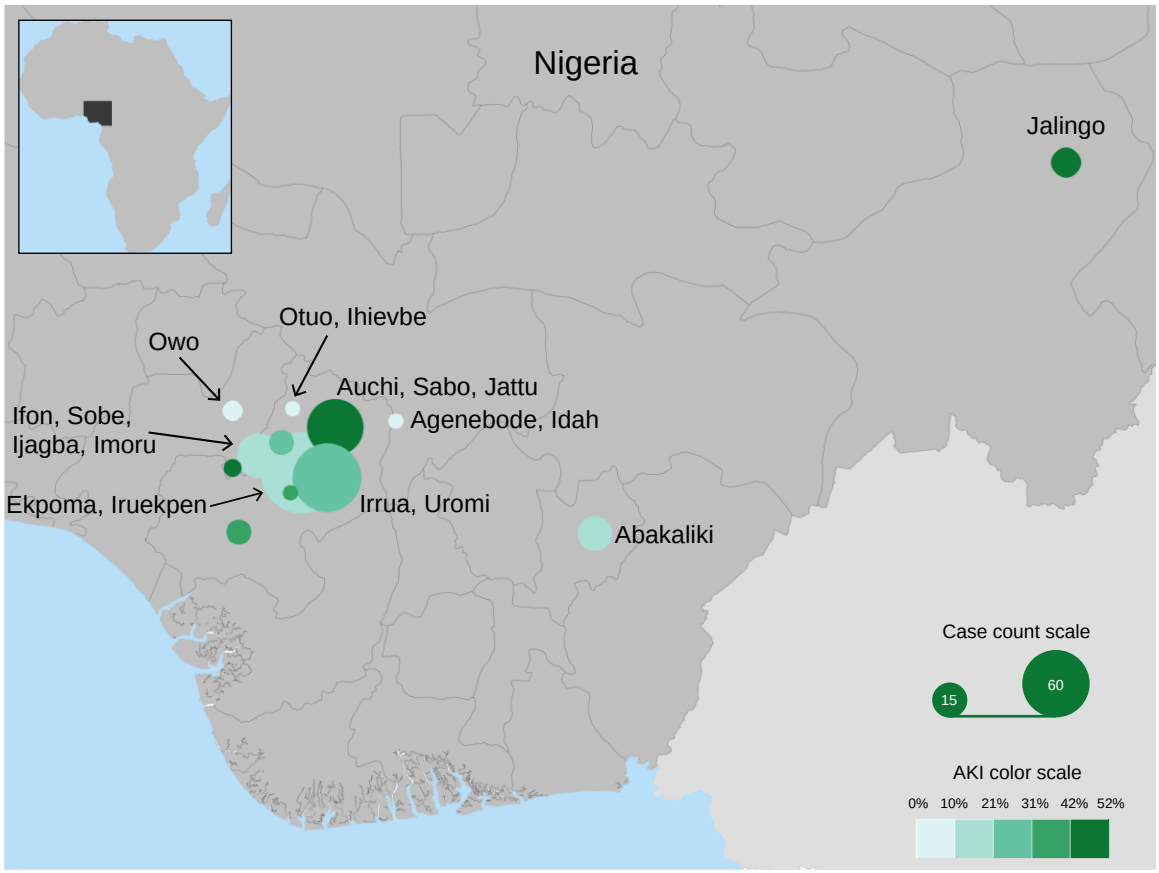
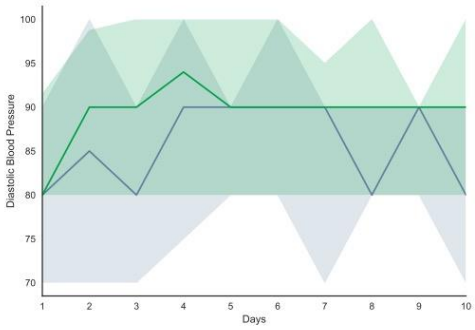
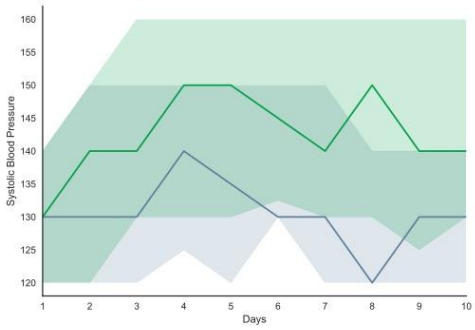
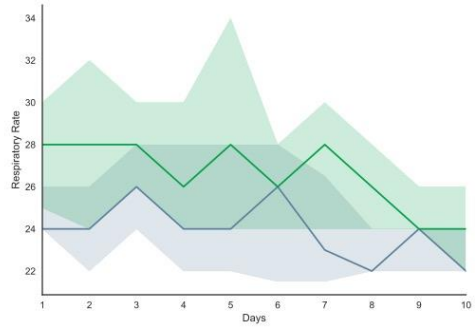
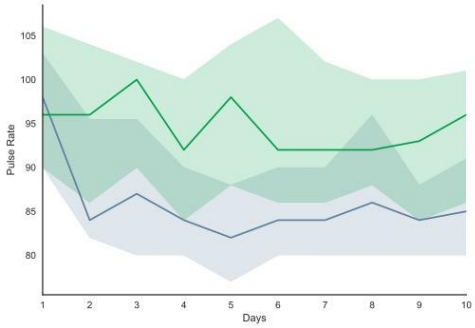

Nigeria
Jalingo
Otuo, Ihievbe
Owo
Auchi, Sabo, Jattu
Agenebode, Idah
Ifon, Sobe,
Ijagba, Imoru
Ekpoma, Iruekpen
Irrua, Uromi
Abakaliki
Case count scale
15
60
AKI color scale
0% 10% 21% 31% 42% 52%

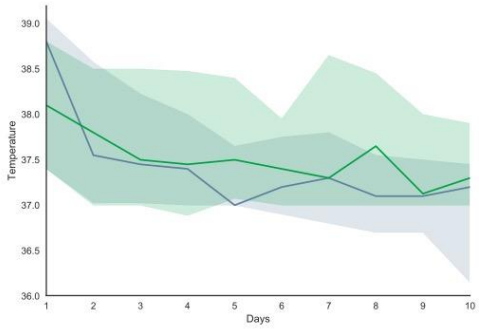
Figure S8

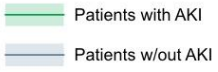












Supplementary Tables

Table S1. Listing of LF case reports published since 1970. Each report includes the year the cases were recorded, the total number of cases, the number of fatalities, the CFR, any observations in the publication that refers to renal involvement, and the first author and year of the publication. The detailed information of each paper is available after the table.

Table S2. Description of logistic regression models. Table A shows the corresponding coefficients, P-values, and odds-ratios for the prognostic model including only laboratory results obtained during admission: AST, Cr, K, total bilirubin (TBIL), platelet count (PLT), and total protein (TPRO), in addition to patient age. Table B shows the coefficients, P-values, and odds-ratios for each term in the prognostic model including only clinical predictors (severe CSN and Face/Neck swelling, jaundice, bleeding, diarrhea and vomiting) at presentation, and patient age. Table C shows the coefficients, P-values, and odds-ratios for each term in the prognostic model including only clinical predictors (temperature, vomiting, bleeding and sore throat) considered by McCormick in 1987. The temperature term is modeled with restricted cubic splines, which results in a linear and a cubic contribution.

Table S3. Performance measures of all prognostic models. The performance of the four models considered in this study (age+clinical+laboratory, age+laboratory-only, age+clinical-only, McCormick's), measured by the adjusted R^2, AUC (apparent and optimism-corrected), and calibration, evaluated on the bootstrap samples.

Table S4. GenBank accession numbers for viral sequences obtained from samples of patients in this cohort. The accession # correspond to the L and S chains of the LASV. Full table can be found in Andersen et al.[14], as "Summary tab: A summary of the generated sequence data" https://ars.els-cdn.com/content/image/1-s2.0-S0092867415008971-mmc2.xlsx. Since Andersen's and our studies were run independently, and the viral sequence analysis study required de-identification of patient information, we were not able to match the clinical metadata with the sequences.

Table S1

Year	Location	Cases	Deaths	CFR (%)	Indications of renal involvement	Reference
1969	Lassa, Nigeria	3	2	66	3+ proteinuria for 1 case.	Frame 1970
1970	Joss, Nigeria	24	12	50	13 patients had ≥2+ albuminuria. Of	Troup 1970,

[14] Andersen KG, Shapiro BJ, Matranga CB, Sealfon R, Lin AE, Moses LM, et al. Clinical Sequencing Uncovers Origins and Evolution of Lassa Virus. Cell 162, 738–750, August 13, 2015. http://dx.doi.org/10.1016/j.cell.2015.07.020

					the 8 patients with 4+ albuminuria, 6 died. Both patients with 3+ died. Death was associated with renal failure in one patient who received plasma transfusion.	Carey 1972, Edington 1972, White 1972
1972	Zorzor, Liberia	10	4	40	1 patient with ≥2+ albuminuria, over 4 for whom the test was performed.	Mertens 1973
1970-2	Eastern Province, Sierra Leone	63*	24	38	4 of 9 patients tested had 2+ or greater proteinuria.	Fraser 1974, Monath 1974
1974	Onitsha, Nigeria	3	1	33		Bowen 1975
1973-76	Panguma, Sierra Leone	156*	22	14	Proteinuria observed in 68 patients.	Keane 1977
1973-76	Segbwema, Sierra Leone	108*	16	14		Keane 1977
1977-9	Two hospitals, 200 miles inland from the capital, Sierra Leone	441	71	16	Proteinuria was common, observed in 2/3 of patients. AST ≫ ALT, meaning that AST might not be generated by the liver. Elevated creatinine phosphokinase (CPK), a predictor of AKI.	McCormick 1987
1978-9	Eastern Province Sierra Leone, Lofa Liberia, neighboring Guinea	42	6	14	Proteinuria, granular casts, and an increase in urobilinogen were frequently seen.	Knobloch 1980
1980-82	Zorzor, Liberia	44	6	13	Observed proteinuria.	Monson 1984
1982	Segbwema, Sierra Leone	5**	0	0	50% of patients presented dysuria.	Sharp 1982
1980-84	Zorzor & Phebe, Liberia	15**	4	26	Minimal albuminuria (1+ in one patient).	Monson 1987
1985	Segbwema, Sierra Leone	32	4	12		Fisher-Hoch 1988
1987	Contracted in Sierra Leone, imported into Japan	1	0	0	Protein and ketone bodies were present in urine. Elevated creatinine phosphokinase (CPK) and hydroxybutyrate dehydrogenase.	Hirabayashi 1988
1980-86	Zorzor, Liberia	246	23	9	3 Nigerian cases with prolonged viremia (18-20 days) developed renal failure, 2 received dialysis. Not observed in patients from Liberia.	Frame 1989
1989	Imo State, Nigeria	34	22	64		Fisher-Hoch 1995

1991	Eastern Sierra Leone	1	1	100		Cummins 1991
1999	Ghana, Ivory Coast, or Burkina Faso (?), imported into Germany	1	1	100		Günther 2000
1996-99	Guinea	22	4	18		Bausch 2001
2000	Ivory Coast, Sierra Leone	2	2	100	Progressive renal dysfunction, renal failure with elevated creatinine levels. High AST/ALT ratio.	Schmitz 2002
2001	Daru, Sierra Leone	1	0	0		ter Meulen 2001
2005-08	Edo State, Nigeria	25	7	28		Ehichioya 2012
2005-08	Nigeria	10	7	70		Ehichioya 2010
2007	Edo State, Nigeria	64	18	28	Late cases of Lassa fever present with hemorrhagic symptoms and renal complications.	Inegbenebor 2010
2008-2009	Edo State, Nigeria	22**	15	71	Passage of coke-colored urine in 4 patients.	Akpede 2010
2008-2009	Edo State, Nigeria	7***	4	57	Oliguria observed in 3 patients.	Okogbenin 2010
2008-2009	Edo State, Nigeria	102	55	54		Okokhere 2010
2008-12	Kenema, Sierra Leone	158	109	69		Shaffer 2014
2009-10	Edo State, Nigeria	198	62	31	Fatal Lassa fever cases had higher creatinine, suggesting renal failure.	Asogun 2012
2011	Tongo, Sierra Leone	2***	0	0	Ongoing proteinuria, peaking on the day of delivery. Normal creatinine and BUN.	Branco 2011
2011	Kenema, Sierra Leone	1	0	0	Significant liver and renal system involvement, but normalization of creatinine levels associated with positive outcome.	Grove 2011
2011	Edo State, Nigeria	5**	2	40	Acute renal failure was an indicator of poor outcome, as it was observed in	Akpede 2012

					the fatal cases.	
2012	Abakaliki, Nigeria	20*	6	30	30% had raised creatinine and 35% had raised urea. All the patients (100%) had proteinuria.	Ajayi 2013
2011-12	Kenema, Sierra Leone	21	8	38	Elevated creatinine.	Roth 2015

Notes

* not all confirmed either serologically or by virus isolation.

** only children (≤15 years old) patients

*** only pregnant patients

Detailed bibliographic information

Frame JD, Baldwin JM, Jr., Gocke DJ, Troup JM. 1970. Lassa fever, a new virus disease of man from West Africa. I. Clinical description and pathological findings. Am J Trop Med Hyg 19:670-676.

Troup JM, White HA, Fom ALMD, Carey DE. 1970. An Outbreak of Lassa Fever on the Jos Plateau, Nigeria, in January–February 1970. The American Journal of Tropical Medicine and Hygiene 19:695-696.

Carey DE, Kemp GE, White HA, Pinneo L, Addy RF, Fom ALMD, Stroh G, Casals J, Henderson BE. 1972. Lassa fever Epidemiological aspects of the 1970 epidemic, Jos, Nigeria. Transactions of the Royal Society of Tropical Medicine and Hygiene 66:402-408.

Edington GM, White HA. 1972. The pathology of lassa fever: A tribute to the late Dr. J.M. Troup. Transactions of the Royal Society of Tropical Medicine and Hygiene 66:381-389.

White HA. 1972. Lassa fever A study of 23 hospital cases. Transactions of the Royal Society of Tropical Medicine and Hygiene 66:390-398.

Mertens PE, Patton R, Baum JJ, Monath TP. 1973. Clinical presentation of lassa fever cases during the hospital epidemic at Zorzor, Liberia, March-April 1972*. The American Journal of Tropical Medicine and Hygiene 22:780-784.

Fraser DW, Campbell CC, Monath TP, Goff PA, Gregg MB. 1974. Lassa Fever in the Eastern Province of Sierra Leone, 1970–1972. The American Journal of Tropical Medicine and Hygiene 23:1131-1139.

Monath TP, Maher M, Casals J, Kissling RE, Cacciapuoti A. 1974. Lassa Fever in the Eastern Province of Sierra Leone, 1970–1972. The American Journal of Tropical Medicine and Hygiene 23:1140-1149.

Bowen GS, Tomori O, Wulff H, Casals J, Noonan A, Downs WG. 1975. Lassa fever in Onitsha, East Central State, Nigeria, in 1974. Bulletin of the World Health Organization 52:599-604.

Keane E, Gilles HM. 1977. Lassa fever in Panguma Hospital, Sierra Leone, 1973-6. British Medical Journal 1:1399-1402.
McCormick JB, King IJ, Webb PA, Johnson KM, O'Sullivan R, Smith ES, Trippel S, Tong TC. 1987. A Case-Control Study of the Clinical Diagnosis and Course of Lassa Fever. Journal of Infectious Diseases 155:445-455.
Knobloch J, Mccormick JB, Webb PA, Dietrich M, Schumacher HH, Dennis E. 1980. Clinical observations in 42 patients with Lassa fever. Tropenmedizin und Parasitologie 31:9.
Monson MH, Frame JD, Jahrling PB, Alexander K. 1984. Endemic Lassa fever in Liberia. I. Clinical and epidemiological aspects at Curran Lutheran Hospital, Zorzor, Liberia. Transactions of the Royal Society of Tropical Medicine and Hygiene 78:549-553.
Sharp PC. 1982. Lassa fever in children. Journal of Infection 4:73-77.
Fisher-Hoch SP, McCormick JB, Sasso D, Craven RB. 1988. Hematologic dysfunction in Lassa fever. Journal of Medical Virology 26:127-135.
Hirabayashi Y, Oka S, Goto H, Shimada K, Kurata T, Fisherhoch SP, McCormick JB. 1988. An Imported Case of Lassa Fever with Late Appearance of Polyserositis. The Journal of Infectious Diseases 158:872-875.
Frame JD. 1989. Clinical Features of Lassa Fever in Liberia. Review of Infectious Diseases 11:S783-S789.
Fisher-Hoch SP, Tomori O, Nasidi A, Perez-Oronoz GI, Fakile Y, Hutwagner L, McCormick JB. 1995. Review of cases of nosocomial Lassa fever in Nigeria: the high price of poor medical practice. BMJ 311:857-859.
Cummins D, Bennett D, Machin SJ. 1991. Exchange transfusion of a patient with fulminant Lassa fever. Postgraduate Medical Journal 67:193-194.
Günther S, Emmerich P, Laue T, Kühle O, Asper M, Jung A, Grewing T, ter Meulen J, Schmitz H. 2000. Imported lassa fever in Germany: molecular characterization of a new lassa virus strain. Emerg Infect Dis 6.
Bausch DG, Demby AH, Coulibaly M, Kanu J, Goba A, Bah A, Condé N, Wurtzel HL, Cavallaro KF, Lloyd E, Baldet FB, Cissé SD, Fofona D, Savané IK, Tolno RT, Mahy B, Wagoner KD, Ksiazek TG, Peters CJ, Rollin PE. 2001. Lassa Fever in Guinea: I. Epidemiology of Human Disease and Clinical Observations. Vector-Borne and Zoonotic Diseases 1:269-281.
Schmitz H, Köhler B, Laue T, Drosten C, Veldkamp PJ, Günther S, Emmerich P, Geisen HP, Fleischer K, Beersma MFC, Hoerauf A. 2002. Monitoring of clinical and laboratory data in two cases of imported Lassa fever. Microbes and Infection 4:43-50.
Ter Meulen J, Lenz O, Koivogui L, Magassouba NF, Kaushik SK, Lewis R, Aldis W. 2001. Short communication: Lassa fever in Sierra Leone: UN peacekeepers are at risk. Tropical Medicine & International Health 6:83-84.

Ehichioya DU, Asogun DA, Ehimuan J, Okokhere PO, Pahlmann M, Ölschläger S, Becker-Ziaja B, Günther S, Omilabu SA. 2012. Hospital-based surveillance for Lassa fever in Edo State, Nigeria, 2005–2008. Tropical Medicine & International Health 17:1001-1004.
Ehichioya DU, Hass M, Ölschläger S, Becker-Ziaja B, Onyebuchi Chukwu CO, Coker J, Nasidi A, Ogugua O-O, Günther S, Omilabu SA. 2010. Lassa Fever, Nigeria, 2005–2008. Emerging Infectious Disease journal 16:1040.
Inegbenebor U, Okosun J, Inegbenebor J. 2010. Prevention of Lassa fever in Nigeria. Transactions of The Royal Society of Tropical Medicine and Hygiene 104:51-54.
Akpede G, Odike A, Okokhere P, Olomu SC, Asogun D, Happi C, Günther S. Prevalence and presentation of Lassa fever in Nigerian Children. International Journal of Infectious Diseases. 2010;14 S1: 76.021;pge e380.
Okogbenin SA, Asogun D, Akpede G, Okokhere P, Günther S, Happi C. New lessons from a case series review of Lassa fever in pregnancy. International Journal of Infectious Diseases. 2010;14 S1: 76.021;pge e380.
Okokhere P, Asogun D, Okogbenin SA. The effect of malaria on the outcome of Lassa Fever. International Journal of Infectious Diseases. 2010;14 S1: 76.021;pge e380.
Shaffer JG, Grant DS, Schiefflin JS, Boisen ML, Goba A, et al. 2104. Lassa Fever in Post-Conflict Sierra Leone. PLOS Neglected Tropical Diseases. 8(3): e2748. doi:10. 1371/journal.pntd.0002748.
Branco LM, Boisen ML, Andersen KG, Grove JN, Moses LM, Muncy IJ, Henderson LA, Schieffellin JS, Robinson JE, Bangura JJ, Grant DS, Raabe VN, Fonnie M, Sabeti PC, Garry RF. 2011. Lassa hemorrhagic fever in a late term pregnancy from northern Sierra Leone with a positive maternal outcome: case report. Virology Journal 8:404.
Grove JN, Boisen ML, Muncy IJ, Henderson LA, Schiefellin JS, Robinson JE, Bangura JJ, Fonnie M, Schoepp RJ, Hensley LE, Seisay A, Fair JN, Garry RF. 2011. Capacity building permitting comprehensive monitoring of a severe case of Lassa hemorrhagic fever in Sierra Leone with a positive outcome: case report. Virolology Journal 8.
Akpede G, Kayode-Adedeji B, Dawodu S. 2012. Manifestations and outcomes of lassa fever in Nigerian children: a case series. Archives of Disease in Childhood 97:A38-A39.
Ajayi NA, Nwigwe CG, Azuogu BN, Onyire BN, Nwonwu EU, Ogbonnaya LU, Onwe FI, Ekaete T, Günther S, Ukwaja KN. 2013. Containing a Lassa fever epidemic in a resource-limited setting: outbreak description and lessons learned from Abakaliki, Nigeria (January–March 2012). International Journal of Infectious Diseases 17:e1011-e1016.
Roth PJ, Grant DS, Ngegbai AS, Schieffelin J, McClelland RS, Jarrett OD. 2015. Factors Associated with Mortality in Febrile Patients in a Government Referral Hospital

in the Kenema District of Sierra Leone. The American Journal of Tropical Medicine and Hygiene 92:172-177.

Table S2A

Variable	*Coefficient (95% CI)*	*OR (95% CI)*	*P-value*
Age	0.034 (0.008, 0.059)	1.40 (1.21, 1.65)	0.009
AST[15]	0.003 (0.000, 0.007)	1.58 (0.53, 2.99)	0.07
Cr[16]	0.173 (0.028, 0.318)	1.41 (1.13, 1.81)	0.02
K[17]	0.877 (0.290, 1.464)	3.41 (1.63, 6.25)	0.004

Table S2B

[15] Aspartate aminotransferase
[16] Creatinine
[17] Potassium

Variable	*Coefficient (95% CI)*	*OR (95% CI)*	*P-value*
Age	0.046 (0.026, 0.067)	1.59 (1.53, 1.72)	<0.0001
Severe CNS[18]	1.399 (0.625, 2.173)	4.05 (3.70, 5.61)	<0.001
Jaundice	2.452 (0.943, 3.961)	11.61 (10.32, 21.32)	0.0015
Bleeding	0.791 (0.076, 1.506)	2.20 (2.01, 2.79)	0.03
F/N Swelling[19]	1.348 (0.472, 2.225)	3.85 (3.68, 5.44)	0.0027
Hematuria	1.192 (-0.059, 2.444)	3.30 (0.75, 7.42)	0.061

Table S2C

Variable	*Coefficient (95% CI)*	*OR (95% CI)*	*P-value*
Temperature	-0.408 (-0.949, 0.134)	NA*	0.14
Temperature'	0.474 (-0.067, 1.016)	NA*	0.086
Sore throat	-0.157 (-0.742, 0.428)	0.85 (0.79, 0.97)	0.6
Bleeding	0.738 (0.112, 1.364)	2.10 (2.05, 2.48)	0.02
Vomiting	-0.451 (-1.049, 0.147)	0.63 (0.59, 0.74)	0.14

* OR is not available for this variable because it corresponds to a non-linear term

Table S3

Statistic	*Age + Clinical + Laboratory*	*Age + Laboratory-only*	*Age + Clinical-only*	*McCormick's*
Adjusted R^2	0.450 (0.371, 0.526)	0.366 (0.290, 0.440)	0.269 (0.204, 0.337)	0.069 (0.043, 0.102)
Corrected AUC	0.865 (0.826, 0.904)	0.851 (0.791, 0.911)	0.776 (0.748, 0.804)	0.547 (0.528, 0.566)
Calibration	0.080 (0.043, 0.118)	0.104 (0.042, 0.166)	0.124 (0.092, 0.157)	0.281 (0.155, 0.408)

[18] Severe central nervous system symptoms
[19] Face and neck swelling

Table S4

SAMPLE	DATE	S SEGMENT GENBANK ACC. #	L SEGMENT GENBANK ACC. #	OUTCOME
ISTH0009	2011	KM821912	KM821911	N/A
ISTH0012	2011	KM821914	KM821913	N/A
ISTH0047	2011	KM821916	KM821915	Died
ISTH0073	2011	KM821918	KM821917	Died
ISTH0230	2011	KM821920	KM821919	Died
ISTH0531	2011	KM821922	KM821921	Died
ISTH0595	2011	KM821924	KM821923	Discharged
ISTH0964	2011	KM821925	N/A	N/A
ISTH1003	2011	KM821927	KM821926	Died
ISTH1038	2011	KM821929	KM821928	Died
ISTH1048	2011	KM821931	KM821930	Discharged
ISTH1058	2011	KM821933	KM821932	Died

ISTH1064	2011	KM821935	KM821934	Discharged
ISTH1069	2011	KM821937	KM821936	Discharged
ISTH1096	2012	KM821939	KM821938	Died
ISTH1107	2012	KM821941	KM821940	N/A
ISTH1111	2011	KM821943	KM821942	Died
ISTH1121	2012	KM821945	KM821944	Discharged
ISTH1129	2012	KM821947	KM821946	Died
ISTH1137	2011	KM821949	KM821948	Died
ISTH2010	2012	KM821951	KM821950	Died
ISTH2016	2012	KM821953	KM821952	Died
ISTH2020	2012	KM821955	KM821954	Died
ISTH2025	2012	KM821957	KM821956	Discharged
ISTH2031	2012	KM821959	KM821958	Died
ISTH2037	2012	KM821961	KM821960	Discharged
ISTH2042	2012	KM821963	KM821962	Discharged
ISTH2046	2012	KM821965	KM821964	Discharged
ISTH2050	2012	KM821967	KM821966	Died
ISTH2057	2012	KM821969	KM821968	Discharged
ISTH2061	2012	KM821971	KM821970	Died
ISTH2064	2012	KM821972	N/A	Discharged
ISTH2065	2012	KM821974	KM821973	Discharged
ISTH2066	2012	KM821976	KM821975	Died
ISTH2069	2012	KM821977	N/A	Discharged
ISTH2094	2012	KM821979	KM821978	Discharged
ISTH2121	2012	KM821980	N/A	Died
ISTH2129	2012	KM821982	KM821981	Died
ISTH2217	2012	KM821984	KM821983	Died
ISTH2271	2012	KM821986	KM821985	Discharged
ISTH2304	2012	KM821988	KM821987	Died
ISTH2312	2012	KM821990	KM821989	Died
ISTH2316	2012	KM821992	KM821991	Discharged
ISTH2334	2012	KM821994	KM821993	N/A
ISTH2358	2012	KM821996	KM821995	N/A
ISTH2376	2012	KM821998	KM821997	Discharged
LASV241	2011	KM822033	KM822032	N/A
LASV245	2011	KM822037	KM822036	N/A
LASV250	2011	KM822041	KM822040	N/A
LASV253	2011	KM822045	KM822044	N/A
LASV254	2011	KM822047	KM822046	N/A
LASV263	2011	KM822051	KM822050	N/A